2024–1408

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

REGENXBIO INC., THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,

Plaintiffs-Appellants

v.

SAREPTA THERAPEUTICS, INC., SAREPTA THERAPEUTICS THREE, LLC,

Defendants-Appellees

Appeal from the United States District Court for the District of Delaware in Case No. 1:20-cv-01226-RGA, Judge Richard G. Andrews

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BRIEF OF DEFENDANTS-APPELLEES SAREPTA THERAPEUTICS, INC. AND SAREPTA THERAPEUTICS THREE, LLC

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July 22, 2024

REPRESENTATIVE CLAIMS

U.S. Patent No. 10,526,617:

1. A cultured host cell containing a recombinant nucleic acid molecule encoding an AAV vp1 capsid protein having

a sequence comprising amino acids 1 to 738 of SEQ ID NO: 81 (AAVrh.10) or

a sequence at least 95% identical to the full length of amino acids 1 to 738 of SEQ ID NO: 81,

wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence.

7. A cultured host cell containing a recombinant nucleic acid molecule comprising

(a) nucleotides 845 to 3058 of SEQ ID NO: 59 or a sequence at least 95% identical to nucleotides 845 to 3058 of SEQ ID NO: 59;

(b) nucleotides 1256 to 3058 of SEQ ID NO: 59 or a sequence at least 95% identical to nucleotides 1256 to 3058 of SEQ ID NO: 59; or

(c) nucleotides 1454 to 3058 of SEQ ID NO: 59 or a sequence at least 95% identical to nucleotides 1454 to 3058 of SEQ ID NO: 59,

wherein the recombinant nucleic acid molecule further comprises a heterologous non-AAV sequence.

Appx384-385.

CERTIFICATE OF INTEREST

I certify that the following information is accurate and complete to the best of my knowledge:

1. **Represented Entities.** Fed. Cir. R. 47.4(a)(1). Provide the full names of all entities represented by undersigned counsel in this case:

   Sarepta Therapeutics, Inc.
   Sarepta Therapeutics Three, LLC

2. **Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities:

   None/Not Applicable

3. **Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities:

   Sarepta Therapeutics, Inc.: None
   Sarepta Therapeutics Three, LLC: Sarepta Therapeutics, Inc.

4. **Legal Representatives.** Fed. Cir. R. 47.4(a)(4). List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court:

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5. **Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a):

No

6. **Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6):

None/Not Applicable

Dated: July 22, 2024

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TABLE OF ABBREVIATIONS

’617 patent	U.S. Patent No. 10,526,617
AAV	adeno-associated virus
Appx__	Appendix page __
Asserted Claims	claims 1-9,12,15, 18-25 of the ’617 patent
Br.	Brief of Regenxbio Inc. and The Trustees of the University of Pennsylvania, dated May 8, 2024
POSA	person of ordinary skill in the art
rAAV	recombinant adeno-associated virus
Regenxbio	Plaintiffs-Appellants Regenxbio Inc. and The Trustees of the University of Pennsylvania
Sarepta	Defendants-Appellees Sarepta Therapeutics, Inc. and Sarepta Therapeutics Three, LLC

STATEMENT OF RELATED CASES

No other appeal from this civil action was previously before this Court or any other appellate court. Counsel for Sarepta is not aware of any other case that will directly affect or be directly affected by the Court's decision in this appeal.

STATEMENT OF THE ISSUE

Whether the District Court correctly granted summary judgment under §101 given the undisputed fact that the DNA sequences recited in the Asserted Claims were isolated from a naturally occurring source – and therefore, are not patent eligible – and the clear admissions of the named inventors and Regenxbio's experts that the Asserted Claims do not reflect any markedly different characteristics that distinguish the claimed compositions from the naturally occurring DNA sequences themselves.

INTRODUCTION

The '617 patent is Regenxbio's attempt to salvage an aging application that became obsolete following the Supreme Court's decision in *Myriad*. In the priority application, filed in 2002, the named inventors disclose the isolation of naturally occurring AAV sequences from tissue samples obtained from non-human primates – including sequences encoding the capsid proteins for the rh.10 variant. The named inventors tout these isolated, naturally occurring sequences as their alleged contribution to the art.

In 2013, more than 10 years after the priority application, the Supreme Court decided *Myriad* – holding that "isolated" DNA sequences are not patent eligible. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 569 U.S. 576, 596 (2013).

This decision foreclosed Regenxbio from obtaining claims to the "isolated" rh.10 sequences in its application.

Not to be deterred, Regenxbio filed the divisional application for the '617 patent in 2017. Regenxbio attempted to sidestep *Myriad* by appending various generic elements to the patent-ineligible rh.10 sequences. But even with these additional elements, the Asserted Claims do not have "markedly different characteristics" that distinguish the claimed compositions from the naturally occurring rh.10 sequences. Thus, they are not patent eligible. *See Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980).

The Asserted Claims are not the result of innovation or any scientific advance. They do not incorporate the naturally occurring rh.10 sequences into a patentable application. Instead, the specification of the '617 patent and the testimony of Regenxbio's witnesses confirm that the additional elements in the Asserted Claims were all well-known and conventional as of the priority date in 2002, and had been widely practiced by persons of ordinary skill in the art – both individually and in combination. As the first named inventor, Dr. Guangping Gao, conceded, "[t]he ***value*** here is [the] ***rhesus 10 sequence***." Appx970:19-971:12 (emphasis added).

At most, the additional elements in the Asserted Claims identify the location of the rh.10 sequences after they have been removed from their naturally occurring source – *i.e.*, they are attached to an unspecified "heterologous non-AAV" sequence

and contained in a generic "cultured host cell." At this level of generality, these admittedly conventional elements reflect no more than the isolation of the rh.10 sequences from the surrounding genetic material in the tissue sample. In essence, the additional elements are just another way of saying that the naturally occurring rh.10 sequences are "isolated." As such, the Asserted Claims fall squarely within the holding in *Myriad* that alleged structural differences resulting from the isolation of naturally occurring DNA sequences – such as the breaking of chemical bonds – are not "markedly different characteristics" that distinguish isolated DNA sequences from ineligible products of nature. *Myriad*, 569 U.S. at 593, 596.

Likewise, the combinations of admittedly conventional elements in the Asserted Claims do not result in any "markedly different" functional characteristics. Regenxbio lists various functions that the claimed cultured host cells allegedly "may" be able to perform. But in this instance, Regenxbio runs afoul of the fundamental principle – recently confirmed by this Court in *ChromaDex* – that the alleged characteristics must be defining features of the claims. Here, Regenxbio's technical expert admits that the Asserted Claims broadly encompass certain cultured host cells that would be "***incapable***" of performing the functions that Regenxbio now contends distinguish the claimed subject matter. Appx1230 at ¶52 (emphasis added). By the admission of Regenxbio's own expert, the alleged functional characteristics are not defining features of the Asserted Claims. Thus, they are

irrelevant to the determination of patent eligibility. *ChromaDex, Inc. v. Elysium Health, Inc.*, 59 F.4th 1280, 1285 (Fed. Cir. 2023).

The analysis of the Asserted Claims is a straightforward application of the "markedly different characteristics" test. *Myriad* forecloses Regenxbio's arguments regarding alleged structural differences that merely reflect the "isolation" of the rh.10 sequences from their naturally occurring source. And the alleged functional differences – which are indisputably not defining features of the Asserted Claims – are irrelevant under *Chakrabarty* and subsequent decisions of this Court. Under the controlling cases, none of the alleged structural or functional differences are "markedly different characteristics" that patentably distinguish the Asserted Claims from the naturally occurring rh.10 sequences. Thus, the Asserted Claims are invalid under §101.

The circumstances in this case epitomize Regenxbio's efforts to sidestep *Myriad* and monopolize the naturally occurring rh.10 sequences. In 2017, when the application for the '617 patent was filed, the priority application from 2002 was aging rapidly – significantly limiting the term for any subsequently issued claims. Regenxbio had failed to commercialize or license any gene therapy product using the rh.10 sequences. In an attempt to monetize this stale application, Regenxbio took aim at Sarepta's research and development of gene therapy products for the treatment of life-threatening muscular dystrophies. However, Sarepta had not yet

completed the clinical testing of any gene therapy product candidate, and had not filed a Biologics License Application ("BLA") with the Food and Drug Administration ("FDA"). Regenxbio was precluded by the Safe Harbor from accusing Sarepta's gene therapy products of infringement while they were still in the pre-BLA stage of research and development. Instead, to avoid the Safe Harbor, Regenxbio pursued claims to cultured host cells "containing" the naturally occurring AAV sequences, rather than any application of the rh.10 sequences in a final product or method of treatment for any disease.

Moreover, Regenxbio understood that Sarepta uses the naturally occurring sequences from a different AAV variant – designated rh.74 – in its research and development. In order to capture Sarepta's rh.74 sequences, Regenxbio drafted the Asserted Claims to encompass not only the naturally occurring rh.10 sequences in its application, but also any naturally occurring AAV sequences that are allegedly "at least 95% identical" to rh.10. However, no scientific advance is reflected in the "at least 95% identical" element. As Dr. Gao testified, no experiments were performed to identify the "at least 95% identical" threshold as having any scientific significance. Appx988:14-16. Instead, as Dr. James Wilson (another named inventor) testified, the 95% limitation for sequence identity was "***driven***" by a discussion with "***patent counsel***." Appx895:23-896:13 (emphasis added).

In 2020, when the '617 patent issued, Regenxbio attempted to leverage the Asserted Claims to stifle Sarepta's efforts to innovate. With less than 3 years of patent term, Regenxbio rushed to file this case in the midst of Sarepta's research and development of its gene therapy product candidates. In response to Regenxbio's attempt to derail its gene therapy program, Sarepta moved to dismiss on the grounds that its activities did not infringe under the Safe Harbor. At oral argument on the motion, Regenxbio conceded that the Asserted Claims do not cover any innovative treatment or final gene therapy product, but instead, are just a "***research tool***" used during the manufacture of AAV vectors. Appx1555 at 37:25-38:22 (emphasis added). As Regenxbio's expert on FDA practices and procedures summed it up, the claimed cultured host cells are a tool – akin to "***a sterile vessel***" – used to contain the naturally occurring rh.10 sequences. Appx1424 at ¶58 (emphasis added).

Never before has this Court or the Supreme Court held that it is sufficient under §101 to simply append conventional elements, without more, to a patent-ineligible law of nature, natural phenomenon, or abstract idea. *See Mayo Collaborative Servs. v. Prometheus Labs., Inc*., 566 U.S. 66, 80-85 (2012). To do so now, as Regenxbio asks, would break with over 40 years of established precedent, starting with *Chakrabarty,* and would eviscerate the holding in *Myriad*. If all that is required for patent eligibility is to append one or more generic elements to a naturally occurring DNA sequence, patent eligibility becomes nothing more than an

exercise in claim drafting. But as the Supreme Court has long cautioned, the difference between patent eligibility and ineligibility depends on more than just the vagaries of "the draftsman's art." *Parker v. Flook*, 437 U.S. 584, 593 (1978). To assume otherwise "would ill serve the principles underlying the prohibition against patents for 'ideas' or phenomena of nature." *Id.*

The Asserted Claims are Regenxbio's attempt to sidestep *Myriad* and patent a basic tool of scientific research by appending various conventional elements to the naturally occurring rh.10 sequences. As such, the Asserted Claims skew the incentives underlying §101 and upset the balance between rewarding genuine scientific advances on the one hand and promoting innovation through research and development on the other. The Asserted Claims attempt to monopolize one of the basic tools of nature – naturally occurring rh.10 sequences – that under the established exceptions to §101 are "manifestations of . . . nature, free to all men and reserved exclusively to none." *Myriad*, 569 U.S. at 589; *Mayo*, 566 U.S. at 71 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co*., 333 U.S. 127, 130 (1948) and citing *Chakrabarty*, 447 U.S. at 309). The judgment should be affirmed.

STATEMENT OF THE CASE

I. The '617 Patent

The '617 patent is titled "Method of Detecting and/or Identifying Adeno-Associated Virus (AAV) Sequences and Isolating Novel Sequences Identified

Thereby." Appx47. In the title, the named inventors identify what they considered to be their contribution to the art – a "method of detecting" AAV sequences and "isolating" those sequences from their naturally occurring source. *Id*.

The '617 patent issued on January 7, 2020, based on a priority application filed on November 12, 2002. Appx47-48. The '617 patent expired on November 12, 2022 – a term of less than 3 years after issuance.

A. The Specification

The '617 patent discloses a method for detecting naturally occurring AAV sequences in mixed DNA samples extracted from primate tissues. Appx166 at 1:57-66. The named inventors used the disclosed method to identify naturally occurring sequences for previously unknown AAV variants – including rh.10. They performed an analysis of tissue samples from non-human primates, including rhesus monkeys, chimpanzees, and baboons. Appx183 at 35:19-26, 35:30-33, 36:16-28; Appx185 at 39:7-10. Altogether, the named inventors isolated DNA sequences for 50 naturally occurring AAV variants. Appx184 at 38:2-3.

The newly-identified AAV sequences are listed in Table 1, which is excerpted and highlighted below. Appx171 at 11:19-22, 11:50-12:43.

TABLE 1

AAV Cap Sequence	Clone Number	Source Species	Tissue	SEQ ID NO (DNA)
Rh.1	Clone 9 (AAV9)	Rhesus	Heart	5
Rh.2	Clone 43.1	Rhesus	MLN	39
Rh.3	Clone 43.5	Rhesus	MLN	40
Rh.4	Clone 43.12	Rhesus	MLN	41
Rh.5	Clone 43.20	Rhesus	MLN	42
Rh.6	Clone 43.21	Rhesus	MLN	43
Rh.7	Clone 43.23	Rhesus	MLN	44
Rh.8	Clone 43.25	Rhesus	MLN	45
Rh.9	Clone 44.1	Rhesus	Liver	46
Rh.10	Clone 44.2	Rhesus	Liver	59
Rh.11	Clone 44.5	Rhesus	Liver	47

In Table 1, the sequences are numbered in order as they were isolated, with a prefix indicating the primate species from which they were derived – *i.e.*, rh.10 is the tenth AAV isolated from a rhesus monkey. Appx185 at 40:9-12.

B. The Asserted Claims

The Asserted Claims recite a natural phenomenon – *i.e.*, naturally occurring DNA sequences encoding vp1, vp2, and vp3 capsid proteins for the rh.10 variant. Claims 1 and 7, which are reproduced on the inside cover, are representative.

The central element in claim 1 is a nucleic acid molecule encoding the vp1 capsid protein of AAV rh.10. The recited amino acid sequence – *i.e.*, amino acids 1 to 738 of SEQ ID NO: 81 – is a naturally occurring sequence that the inventors deduced from the nucleic acid sequence they isolated from a tissue sample taken from a rhesus monkey. Appx890:16-19; Appx969:21-970:17. The recited amino acid sequence is exactly the sequence of the vp1 capsid protein for rh.10 that is found in nature. Appx773:24-775:2; Appx1267 at ¶322.

Like claim 1, the central element of claim 7 is a naturally occurring DNA sequence – in this case, the sequence of nucleotides identified at SEQ ID NO: 59. The portions of the nucleotide sequence recited in elements (a), (b), and (c) encode the vp1, vp2, and vp3 capsid proteins for the naturally-occurring rh.10 variant, respectively. This sequence was extracted from a tissue sample taken from a rhesus monkey. Appx170 at 9:8-17; Appx171 at 11:53-12:42 (Table 1). And like the amino acid sequence, the recited nucleotide sequence encoding the rh.10 capsid proteins is exactly the same sequence found in nature, without modification.

The additional elements in the Asserted Claims locate the naturally occurring rh.10 sequences in a "recombinant nucleic acid molecule" that is unspecified and includes a "heterologous non-AAV sequence," which is also unspecified. *See, e.g.*, Appx384 (claim 1); Appx385 (claim 7). The "heterologous non-AAV" has no recited properties. It need not perform any function or encode any genetic information. It is simply a non-AAV sequence from any source that is attached to the naturally occurring rh.10 sequence in the same nucleic acid molecule.

The nucleic acid molecule can be a "plasmid" (a circular piece of DNA or RNA) or any other form (such as a linear molecule). *See* Appx385 (claims 22-25). The nucleic acid molecule can also include other, known AAV sequences, such as an "AAV2 rep gene." Appx385 (claims 18-21).

Finally, the recombinant nucleic acid molecule is placed in "a cultured host cell," that is again unspecified. Appx384 (claim 1); Appx385 (claim 7). The cultured host cells have no recited properties or other characteristics. They do not need to be able to read or express the genetic information in the nucleic acid sequences encoding the capsid proteins for AAV rh.10. According to the plain language of the Asserted Claims, the cultured host cells have no function other than to "***contain***" the recombinant nucleic acid molecule comprising the naturally occurring rh.10 sequences. This is reflected in the use of the transitional phrase "***containing***" in each Asserted Claim. Appx384-385.

II. Sarepta Therapeutics

Sarepta Therapeutics is a biotechnology company at the forefront of precision genetic medicine. Sarepta currently has over 40 therapies in various stages of development for the treatment of rare diseases. Sarepta is a recognized leader in the development of treatments for Duchenne muscular dystrophy ("DMD")[1] and limb-

[1] DMD is a rare genetic disease that predominantly affects males, with symptoms typically becoming noticeable between the ages of 3 and 5. DMD is caused by a mutation in the gene coding for dystrophin – an essential protein that plays a pivotal role in muscle structure, function, and preservation. DMD causes the muscles in the body to become weak and damaged over time and is eventually fatal. www.sarepta.com/disease-areas/duchenne-muscular-dystrophy.

girdle muscular dystrophy ("LGMD").[2] Sarepta currently has four FDA-approved products on the market – including Elevidys® – the first gene therapy for the treatment of DMD, which was approved on June 22, 2023 – seven months after the '617 patent expired.[3] By contrast, Regenxbio, has not successfully developed any commercial products of its own – let alone any products that use the naturally occurring rh.10 sequences in any practical application, such as a gene therapy product for the treatment of a specific disease.

III. The District Court Proceedings

Regenxbio filed this case on September 15, 2020. Appx1535. Regenxbio alleged infringement of the cultured host cells that Sarepta used to make at least eight gene therapy products in development – including Sarepta's gene therapy candidate, SRP-9001, which is now FDA-approved and marketed as Elevidys®. Appx1540 at ¶26; Appx1542-1543 at ¶34 n.2. Regenxbio did not allege infringement by any final gene therapy product.

Likewise, Regenxbio did not allege that Sarepta used the rh.10 sequences recited in the Asserted Claims. As Regenxbio acknowledged, Sarepta used

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[2] LGMD refers to a group of distinct diseases that cause weakness and wasting of the muscles. There are more than 30 LGMD subtypes, each with a unique underlying genetic cause and wide variation in their severity. www.sarepta.com/disease-areas/limb-girdle-muscular-dystrophy.

[3] *See* https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-certain-patients-duchenne-muscular-dystrophy.

sequences from a different, naturally occurring AAV variant – designated rh.74. Appx1540-1541 at ¶¶29-30; Appx1542-1543 at ¶34 n.2. Sarepta licenses the cited gene therapy products, including the AAV rh.74 vector, from its longtime research partner Nationwide Children's Hospital ("NCH") in Columbus, Ohio – where the rh.74 variant was first discovered. Appx1569; Appx1600 at 13:28-14:8 (Example 1); *see also* Appx925:19-926:22; Appx927:11-928:3.

The rh.74 variant is not disclosed in the '617 patent. Appx171 at 11:50-51, 11:53-12:43 (Table 1). As Dr. Gao and Dr. Wilson both confirmed, they did not isolate the sequences for rh.74. Appx928:23-929:3; Appx930:1-5; Appx931:5-8; Appx1007:3-1008:9; Appx1010:3-6.

Regenxbio alleged that the rh.74 sequences infringe the Asserted Claims because they are "at least 95% identical" to the recited rh.10 sequences. Appx1540-41 at ¶¶27-29. Thus, according to Regenxbio, the Asserted Claims encompass more than just the naturally occurring rh.10 sequences isolated by the named inventors. The Asserted Claims also encompass other naturally occurring AAV sequences, such as rh.74, that according to Regenxbio are allegedly "at least 95% identical" to

the naturally occurring rh.10 sequences – regardless of whether the named inventors isolated them or not.[4]

A. Regenxbio's Characterization of the Claimed Cultured Host Cells as a "Research Tool"

On November 4, 2020, Sarepta moved to dismiss the Complaint on the grounds that its research and development activities were protected by the Safe Harbor under §271(e)(1), and therefore, did not infringe the '617 patent. Appx1639-1640. In response, Regenxbio argued that Sarepta's use of the naturally occurring DNA sequences in the accused cultured host cells was not covered by the Safe Harbor. Appx1660. Regenxbio analogized the accused cultured host cells to "***research tools or devices***" that are not subject to FDA approval. Appx1665 (quoting *Momenta Pharms., Inc. v. Teva Pharms. USA Inc.*, 809 F.3d 610, 619 (Fed. Cir. 2015)) (emphasis added). At oral argument, Regenxbio reiterated this analogy between the accused cultured host cells and research tools:

> THE COURT: So do you think the -- are the cultured cells here – they're not research tools, are they?

[4] The timing of the application for the '617 patent strongly suggests that the inclusion of the "at least 95% identical" element was an attempt to ensnare the rh.74 sequences. Regenxbio filed the application that led to the '617 patent on October 13, 2017 – nearly 15 years after the earliest priority application. Appx47. By that time, NCH had published the rh.74 sequences first identified by researchers in its labs. Appx1600 at 13:67-14:2; Appx1604-1607 at SEQ ID NOS: 1, 2. And Sarepta had announced its research collaboration with NCH to develop gene therapies for the treatment of DMD using NCH's rh.74 vector platform. *See* Appx1613-1615.

> MS. MORRISON: I think they are in the context of how the cases define "research tools" in that they are used in the development of SRP-9001. . . .

Appx1555 at 37:25-38:6.

Similarly, during discovery, Regenxbio's expert on FDA practices and procedures, Erika Lietzan, characterized the accused cultured host cells as merely a tool used during the manufacturing process. Appx1424 at ¶58. Ms. Lietzan analogized the cultured host cells to a container for storing DNA sequences – similar to "the '***sterile vessel***' used to store the eluted plasma DNA during the process" for making Sarepta's gene therapy products. *Id*. (emphasis added).[5]

B. The District Court's Judgment That the Asserted Claims Are Invalid for Patent-Ineligible Subject Matter

In its summary judgment decision, the District Court applied both the "markedly different characteristics" test in *Chakrabarty* and the two-part test in *Alice*/*Mayo*, and under both standards, found the Asserted Claims in this case deficient. The District Court grounded its decision on key admissions from Regenxbio and its expert regarding the scope and nature of the Asserted Claims.

The District Court acknowledged the undisputed fact that the rh.10 sequences in the Asserted Claims are exactly the same sequences that occur in nature. Appx10.

[5] The District Court denied Sarepta's motion to dismiss. But in light of the District Court's subsequent ruling that the Asserted Claims are invalid under §101, the Safe Harbor decision is not an issue in this appeal. *See* Appx17-18.

"Plaintiffs do not suggest that the isolated rh.10 sequences are any different from those found in nature," and "isolation on its own is insufficient to create patent-eligible subject matter." *Id*. (citing *Myriad*, 569 U.S. at 596).

Next, the District Court considered the element "heterologous non-AAV sequence," and concluded that this additional element did not reflect any "markedly different characteristics" of the claimed culture host cells. *See* Appx9-10. As Regenxbio admitted during oral argument, the "heterologous non-AAV sequence" in the Asserted Claims can be any non-AAV sequence, including DNA sequences that occur in nature. *See* Appx9 n.2.

The District Court analogized the combination of a naturally occurring rh.10 sequence with a naturally occurring "non-AAV" sequence to *Funk Brothers*, where a mixture of naturally occurring bacteria was found to be patent ineligible. Appx9-10. The District Court concluded that the combination of one naturally occurring DNA sequence and another naturally occurring DNA sequence, without more, is insufficient under *Funk Brothers* to render the Asserted Claims patent eligible. Appx10. As the District Court explained, "Plaintiffs . . . do not argue that the claimed invention's non-AAV sequence or any other elements have been altered from their naturally occurring counterparts." *Id*. "Without some change, the mere fact that the '617 patent's inventors combined natural products and put them in a host cell does not make the invention patentable under §101." *Id*.

The only allegedly distinguishing characteristic that Regenxbio identified below is that the claimed cultured host cells "***may***" be used to make rAAV vectors for gene therapy applications. However, as the District Court recognized, under *Chakrabarty* and subsequent cases, any "markedly different characteristics" for patent eligibility must be defining features of the claims. *See* Appx11. The District Court explained that the ability to make rAAV vectors is not a required feature of the Asserted Claims, and therefore, is not a "markedly different characteristic" that distinguishes them from the naturally occurring rh.10 sequences. *Id*.

In reaching this conclusion, the District Court relied on the admissions of Regenxbio's technical expert, Dr. Paola Leone. Dr. Leone conceded that "some of the claimed embodiments cannot even be used for gene therapy." *Id*. As Dr. Leone explained, certain cultured host cells within the Asserted Claims are not able to express the rh.10 sequences, and as such, "would be ***incapable*** of creating a final gene therapy product." Appx11-12 (emphasis added). Thus, the only feature identified by Regenxbio in support of patentability is not actually a defining feature of the Asserted Claims. As the District Court concluded, the Asserted Claims "simply do not reflect the distinction [Regenxbio] rel[ies] on." Appx12.

Finally, the District Court noted that even if the Asserted Claims cover certain cultured host cells that may be used to make rAAV, that is still not enough for patentability. The District Court explained that "[e]ven if some embodiments of the

claimed invention have utility for gene therapy, that only means the claims cover both eligible and ineligible subject matter. Such claims are not patentable." *Id.* (citing *ChromaDex*, 59 F.4th at 1285).

The District Court also analyzed the Asserted Claims under the two-part *Alice/Mayo* test. For Step 1, the District Court concluded that the Asserted Claims are "directed to" unpatentable subject matter for the reasons discussed above with respect to the "markedly different characteristics" analysis under *Chakrabarty*. *Id.* For Step 2, the District Court concluded that the Asserted Claims "lack an inventive concept that could transform the claimed invention into patent-eligible subject matter." *Id.* As the District Court explained, the additional elements reflect nothing more than "well-understood, routine, and, conventional" activity – according to the '617 patent itself. Appx12-13. Notably, in its opposition to summary judgment, Regenxbio did not argue that the additional elements of the Asserted Claims reflect any "inventive concept." *See* Appx13. Thus, by Regenxbio's own admission, the Asserted Claims are not patent eligible at Step 2.

As the District Court determined, under both *Chakrabarty* and *Alice/Mayo*, the result is the same. In light of the undisputed facts, the Asserted Claims are not patent eligible. The District Court correctly granted summary judgment.

SUMMARY OF THE ARGUMENT

Regenxbio's arguments are untethered to any applicable precedent. Instead, Regenxbio argues that the Asserted Claims are patentable because they are "non-natural," the product of "genetic engineering," or "made in the laboratory." But those arguments are based on no standard of patent eligibility that this Court or the Supreme Court has ever adopted. In fact, Regenxbio's arguments are foreclosed by the controlling cases on patentability for the Asserted Claims.

Under *Myriad*, the Asserted Claims do not reflect the creation of a "new" composition with "markedly different characteristics." *See Myriad*, 569 U.S. at 590-91. As *Myriad* explains, structural differences resulting from the isolation of the rh.10 sequences from the surrounding genetic material – such as the breaking of chemical bonds – are not sufficient for patent eligibility. *See id.* at 593. Here, the additional elements – reciting the location of the isolated rh.10 sequences – merely reflect the separation of the DNA sequences from their natural source. At bottom, the additional elements are just another way of saying that the naturally occurring rh.10 sequences have been "isolated." Under *Myriad*, such elements do not reflect "markedly different" structural characteristics that distinguish the isolated rh.10 sequences from ineligible products of nature. *See id.* at 591, 595.

Under *Chakrabarty*, the alleged functional characteristics are irrelevant to patent eligibility. *See Chakrabarty*, 447 U.S. at 310. Regenxbio identifies various

characteristics that the claimed cultured host cells ***may or may not*** have. But that is insufficient for "markedly different characteristics." Regenxbio's arguments conflict with *Chakrabarty* and subsequent cases, including *ChromaDex*, that alleged characteristics must ***necessarily*** be defining features of the claims. *See id*. at 305; *ChromaDex*, 59 F.4th at 1285. Under the correct standard, Regenxbio's cited characteristics, which are admittedly ***not*** defining features of the Asserted Claims, are not relevant to the determination of patentability.

The Court need go no further than this to conclude that the Asserted Claims are patent ineligible. However, the outcome is the same if the Asserted Claims are analyzed for "markedly different characteristics" using the reasoning in *Funk Brothers* or whether they are analyzed according to the two-part test in *Alice*/*Mayo*. The Asserted Claims are not patent eligible under any analysis. These cases provide additional, independent bases to affirm the judgment.

Under *Funk Brothers*, the combination in the Asserted Claims of two naturally occurring DNA sequences packaged in a conventional "cultured host cell" is not patent eligible. There is no dispute that the "heterologous non-AAV" sequences in the Asserted Claims include naturally occurring sequences. Merely combining two naturally occurring DNA sequences in the same "cultured host cell" container, without more, does not result in any "markedly different characteristics" that

patentably distinguish the Asserted Claims from the naturally occurring sequences themselves. *See Funk Bros.*, 333 U.S. at 131-32.

Likewise, applying the two-part test in *Alice*/*Mayo*, the Asserted Claims are not patent eligible. Under Step 1, the Asserted Claims are "directed to" the unpatentable rh.10 sequences, for the reasons discussed above. Under Step 2, the additional elements in the Asserted Claims add no "inventive concept" that transforms the naturally occurring rh.10 sequences into patentable subject matter. Regenxbio has never attempted to rebut the undisputed facts underlying this conclusion. Thus, the Asserted Claims fail to pass the minimum threshold for patent eligibility under *Alice*/*Mayo* as well.

Regenxbio attempts to analogize the claimed cultured host cells to cDNA. But there is no dispute. The rh.10 sequences in the Asserted Claims are not cDNA. Indeed, the named inventors did not make changes to the naturally occurring rh.10 sequences disclosed in the '617 patent. On the contrary, the named inventors went to great lengths to ensure that the rh.10 sequences they isolated using their PCR method were copied ***exactly*** as they occur in nature. Again, Regenxbio's argument simply contradicts the logic and reasoning in *Myriad*.

In all of its arguments, Regenxbio never actually identifies what it believes to be the patentable invention in the Asserted Claims. Unlike most patentees who eagerly explain their alleged contribution to the art, the reluctant patentees in this

case avoid any discussion of what the named inventors actually did beyond isolating the naturally occurring rh.10 sequences. No matter how Regenxbio attempts to deflect attention from this basic inquiry, the inescapable conclusion is that there is nothing in the Asserted Claims that reflects a markedly different characteristic or patentable advance in the art.

This case is not a close call. Regenxbio disputes no material issue of fact. And its arguments for patent eligibility require the Court to break with some of the most fundamental principles underlying §101. Evaluated under the applicable standards set forth in this Court's and the Supreme Court's settled decisions, the undisputed facts demonstrate that the Asserted Claims are not patent eligible.

STANDARD OF REVIEW

This Court reviews the grant of summary judgment under the law of the regional circuit, in this case the Third Circuit – which reviews issues of summary judgment *de novo*. *ChromaDex*, 59 F.4th at 1282.

Patent eligibility under §101 is a question of law that this Court also reviews *de novo*. *CareDx, Inc. v. Natera, Inc.*, 40 F.4th 1371, 1376 (Fed. Cir. 2022).

ARGUMENT

The Supreme Court has "set forth a [two-step] framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those

that claim patent-eligible applications of those concepts." *Alice Corp. Pty. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014) (citing *Mayo*, 566 U.S. at 77-78).

First, in Step 1, the claims are evaluated to determine whether they are "directed to" a patent ineligible concept. *Id*. This step involves an analysis of "the focus of the claimed advance over the prior art" to determine if the claim as a whole is "directed to" excluded subject matter. *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1375-76 (Fed. Cir. 2016). The inventors' own description of their "discovery" as a natural phenomenon or law of nature is particularly compelling evidence that Step 1 is satisfied. *See, e.g.*, *Roche Molecular Sys. v. Cepheid*, 905 F.3d 1363, 1371-72 (Fed. Cir. 2018).

Second, in Step 2, the claims are evaluated to determine whether the additional elements add an "inventive concept" to ensure that the patent in practice amounts to "significantly more" than the natural phenomenon itself. *Alice Corp.*, 573 U.S. 217-18. In making this assessment, the claim elements should be considered individually and in combination to determine whether the additional elements "transform the nature of the claim" into something patent eligible. *Id*. at 217.

Composition claims that recite products of nature are not patent eligible unless they have "markedly different characteristics." *Chakrabarty*, 447 U.S. at 310. Such claims must reflect the creation of a "new" composition with "markedly different

characteristics" that distinguish the recited compositions from the patent-ineligible natural products themselves. *Myriad*, 569 U.S. at 590-91.

It is not enough to simply append "conventional" elements, specified "at a high level of generality," to a patent-ineligible law of nature, natural phenomenon, or abstract idea. *Mayo*, 566 U.S. 82. The claims must have additional features that "provide practical assurance" that they are "more than a drafting effort designed to monopolize" the unpatentable subject matter itself. *Id*. at 77. Concessions that the additional elements reflect nothing more than what was already conventional in the art – such as statements in the specification or admissions of the named inventors – are hallmarks of patent ineligibility. *See id*. at 79-80; *CareDx*, 40 F.4th at 1378-79.

I. Supreme Court Precedent Forecloses Regenxbio's Arguments Based on Inapplicable Standards of Patent Eligibility

Throughout its brief, Regenxbio ignores the applicable standards for patentability, and instead, argues that the cultured host cells in the Asserted Claims are "non-natural," involve "human intervention," were made "in the laboratory," and are "genetically engineered." Br. at 8-9, 19, 23, 25, 31, 38-39. But no court has ever identified any of those things as sufficient, or even relevant, to patent eligibility.

Indeed, the Supreme Court in *Myriad* determined that these things are ***not*** the correct focus of the inquiry. As the Court acknowledged, "isolated" DNA sequences are "non-natural" by definition. *Myriad*, 569 U.S. at 593 ("[I]solating DNA from the human genome severs chemical bonds and thereby creates ***a nonnaturally***

occurring molecule.") (emphasis added). They have been separated from their natural environment and other components associated with them in their natural source. *Id*. at 596. During this process, chemical changes are made to the DNA molecule, such as the breaking of chemical bonds. *Id*. at 593. Yet, despite all of these "non-natural" characteristics and extensive manipulations in the laboratory, "isolated" DNA sequences are not patent eligible. *Id*. at 596.

Similarly, in *Roslin*, the cloned mammals recited in the claims were the product of "genetic engineering," but that fact was not determinative under §101. The claimed subject matter was still not patent eligible because the cloned mammals had no "markedly different characteristics" compared to their naturally occurring counterparts. *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333, 1337 (Fed. Cir. 2014). The analysis in both *Myriad* and *Roslin* demonstrates that Regenxbio's arguments are premised on incorrect legal standards.

Regenxbio never grapples with the logic or reasoning in *Myriad* why "isolated" DNA sequences are not patentable or how that reasoning is determinative of the issue of patent eligibility in this case. Instead, Regenxbio pays lip service to the "markedly different characteristics" test under *Chakrabarty* by identifying alleged differences between the Asserted Claims and the rh.10 sequences as they exist in nature – *e.g*., attached to a "heterologous non-AAV" sequence and contained in a "cultured host cell" – none of which are "markedly different characteristics" as

is required for patentability. Regenxbio asks this Court to apply a "non-natural," "human intervention," "genetically engineered" standard to the Asserted Claims – a standard of patentability that this Court and the Supreme Court have never adopted. Regenxbio's arguments are essentially a repudiation of *Myriad* – which has been the established standard for claims reciting DNA sequences for over a decade.

II. The Asserted Claims Fall Squarely Within the Established Exception to Patentability for Isolated DNA Sequences

Regenxbio has attempted to sidestep *Myriad* by appending various conventional elements to the naturally occurring rh.10 sequences. But even with these additional elements, the Asserted Claims are not a "new" composition with "markedly different characteristics" – as is required for patentability. *See Myriad*, 569 U.S. at 590-93.

A. There Is No Dispute that the rh.10 Sequences Are Recited in the Asserted Claims Exactly as They Are Found in Nature

The DNA sequences recited in the Asserted Claims are the strings of nucleic acids encoding the vp1, vp2, and vp3 capsid proteins of the naturally occurring AAV rh.10 variant. This is confirmed by the '617 patent itself and the testimony of the named inventors (Dr. Gao, Dr. Wilson, and Mr. Alvira), as summarized below.

- The named inventors testified that the nucleic acid sequence encoding the rh.10 capsid proteins was isolated from a naturally occurring source – a tissue sample from a rhesus monkey. Appx847:11-13; Appx850:12-15; Appx890:11-15; Appx892:11-14; Appx903:19-904:9; Appx905:2-906:2; Appx943:20-944:13; Appx961:14-24; Appx964:12-

17; Appx969:3-6; Appx979:11-980:7; Appx992:12-994:17; Appx1038:4-1041:2.

- Dr. Gao and his colleagues deduced the amino acid sequence for the rh.10 capsid proteins from the isolated nucleic acid sequence. Appx890:16-19; Appx962:2-9, Appx964:19-966:10; Appx969:21-970:17; Appx1683:18-1685:2.

- Dr. Wilson and his colleagues determined that the isolated nucleic acid sequence came from infection with a naturally occurring AAV virus having capsid proteins with the deduced amino acid sequence. Appx848:9-850:11; Appx1034:6-23.

The named inventors did not change the naturally occurring rh.10 sequences. As Mr. Alvira explained, the named inventors performed validation experiments to ensure that their method of isolation was free from artifacts and copied the nucleic acid sequences ***exactly*** as they are found in nature. Appx1027:8-1028:14, Appx1030:9-1034:23.

B. The Asserted Claims Do Not Have "Markedly Different" Structural Characteristics From The Naturally Occurring rh.10 Sequences

In *Myriad*, the Supreme Court analyzed claims reciting "isolated" DNA sequences encoding the human BRCA1 and BRCA2 genes. *Myriad*, 569 U.S. at 590-91. The Court determined that none of the alleged structural differences in the "isolated" DNA reflect the creation of a "new" composition with "markedly different characteristics" compared to the sequences as they exist in nature. *Id*. at 590-93. The Court held that "isolated" DNA is not rendered patentable simply because it has been separated from the "surrounding genetic material." *Id*. at 596.

Here, the named inventors did not "create or alter any of the genetic information" encoded in the rh.10 sequences. *Id*. at 590. Like the "isolated" DNA in *Myriad*, the "location and order" of the nucleic acids in the rh.10 sequences "existed in nature" before the named inventors found them. *Id*. Nor are the Asserted Claims "saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule." *Id*. at 593. As in *Myriad*, the Asserted Claims "***focus on the genetic information***" encoded in the naturally occurring rh.10 sequences. *Id*. (emphasis added).

The additional elements specifying where the rh.10 sequences are located after isolation – *i.e.*, attached to an unspecified "heterologous non-AAV" sequence and contained in a conventional "cultured host cell" – do not change that focus. Like the term "isolated" in *Myriad*, the additional elements in the Asserted Claims all relate to the separation of the naturally occurring rh.10 sequences from the surrounding genetic material. At the level of generality with which they are claimed, the additional elements reflect nothing more than the fact that the recited sequences have been "isolated" from their natural source – which *Myriad* instructs is not sufficient for patentability. *Id*. at 593.

At this level of generality, the additional elements in the Asserted Claims merely recite where the naturally occurring rh.10 sequences are stored in their isolated form – similar to a test tube. *See* Appx1091-92 at ¶¶55-56. However, a

claim to an isolated DNA contained in a test tube does not have "markedly different characteristics." The claim is still fundamentally directed to the isolated DNA – which is not patentable subject matter. *See Myriad*, 569 U.S. at 590, 593. Indeed, at oral argument, Regenxbio conceded that merely "containing" the isolated rh.10 sequences in a test tube is not sufficient for patentability. Appx1450:10-1451:4. As Regenxbio conceded, "[t]hat's ***essentially an isolated nucleic acid sequence***. *Myriad* says those are ***patent ineligible***." Appx1450:16-17 (emphasis added).

C. The Nucleic Acid Sequences in the Asserted Claims Are Not Analogous to cDNA

Regenxbio argues that the combination of a naturally occurring rh.10 sequence and an unspecified "heterologous non-AAV" sequence is patentably distinct from the "isolated" sequences on their own. Br. at 26-28. Here, Regenxbio strains to analogize the "recombinant nucleic acid molecule" in the Asserted Claims to the patent-eligible cDNA in *Myriad*. *Id*. There is no analogy to be made.

In *Myriad*, the Court held that claims to cDNA are patent eligible because "creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring," and in that instance, "the lab technician ***unquestionably creates something new***. . . ." *Myriad*, 569 U.S. at 594-95 (emphasis added). An exons-only cDNA is "something new" because natural DNA also contains non-coding sequences called "introns," which are removed from the sequence for cDNA. *Id*. at 581. The Court recognized, however, that cDNA was not "new" on account

of its other structural differences from naturally occurring molecules – such as the substitution of the nucleotide base thymine in cDNA in place of uracil in the naturally occurring mRNA sequences from which cDNA is made. *See id*. The Court also acknowledged the limits of its decision – noting an important exception, "insofar as very short series of DNA may have no intervening introns to remove when creating cDNA." *Id*. at 595. "In that situation, a short strand of cDNA may be ***indistinguishable from natural DNA***," and therefore, not patent eligible. *Id*.

The reasoning in *Myriad* for cDNA does not apply here. The rh.10 sequences are recited exactly as they are found in nature. Attaching an unspecified "heterologous non-AAV" sequence to the naturally occurring rh.10 sequence does not change that. No changes to the location or order of nucleotides in the rh.10 sequences have been made. No introns or other elements have been removed. The genetic information is exactly the same. Simply attaching a generic "heterologous non-AAV" DNA to the naturally occurring rh.10 sequence is no more transformative than "isolated" DNA or the patent-***ineligible*** short strands of cDNA in *Myriad* having "no intervening introns to remove." *Id*.

Indeed, during prosecution of the '617 patent, the Examiner expressly considered the applicant's amendment of the pending claims to recite a "recombinant" nucleic acid molecule and concluded that this additional term did not overcome an earlier rejection under §101. *See* Appx650-656. The Examiner found

that merely incorporating the naturally occurring rh.10 sequences into a generic "recombinant" nucleic acid molecule – such as by attaching an unspecified "heterologous non-AAV" sequence – does not reflect the creation of a "new" DNA with "markedly different characteristics." *Id*.

As the Examiner explained, "the term 'recombinant' is not considered to distinguish the products of [the pending claims] from naturally occurring nucleic acids or proteins as the products ***still have the same structure or series of nucleotides or amino acids***." Appx654 (emphasis added). The Examiner observed that the pending claims recited "AAV rh.10 nucleic acid that is identical to naturally occurring nucleic acid and does not show a difference in characteristics between the claimed nucleic acid and naturally occurring nucleic acid." *Id*. The Examiner concluded that the claims "recite ***a nature-based product limitation that does not exhibit markedly different characteristics from its naturally occurring counterpart***. . . ." *Id*. (emphasis added). Thus, Regenxbio's attempted analogy to cDNA conflicts with the Examiner's express determination during prosecution that merely reciting the naturally occurring rh.10 sequences in a generic "recombinant" nucleic acid molecule is not sufficient for patentability.

Finally, Regenxbio argues that the cDNA sequences in *Myriad* were patent eligible, even though the claims did not recite any functional characteristics or potential utility. Br. at 40-41. Here, Regenxbio attempts to bolster its argument

that alleged functional characteristics need not be defining features of the Asserted Claims. But again, the analysis of cDNA in *Myriad* does not apply. Contrary to Regenxbio's argument, *Myriad* does not address functional differences because it was not necessary for the analysis of patent eligibility given the "markedly different characteristics" already present in the structure of cDNA. Here, by contrast, no such distinguishing structural characteristics are found in the Asserted Claims.

D. The Asserted Claims Do Not Have "Markedly Different" Functional Characteristics

Regenxbio concedes that none of the alleged functional characteristics are defining features of the Asserted Claims. As this Court has "repeatedly held," "features that are not claimed are ***irrelevant***" to the analysis of patent eligibility and should be disregarded. *American Axle & Manufacturing, Inc. v. Neapco Holdings LLC*, 967 F.3d 1285, 1293 (Fed. Cir. 2020) (collecting cases) (emphasis added).

1. Regenxbio Has Waived Its Arguments Regarding Characteristics That It Did Not Raise in the District Court

Regenxbio identifies at least four characteristics that it contends functionally distinguish the Asserted Claims. Br. at 14, 35. In the District Court, however, Regenxbio identified only a single functional characteristic – the alleged ability of the claimed cultured host cells to make rAAVs for gene therapy. *See* Appx579, Appx583. Regenxbio did not identify any other functions. "The general rule is that this court does not consider arguments not raised below." *Celsis in Vitro, Inc. v.*

Cellzdirect, Inc., 664 F.3d 922, 931 (Fed. Cir. 2012). Thus, Regenxbio's arguments regarding additional functional characteristics are waived. *Eolas Techs. Inc. v. Amazon.com, Inc.*, No. 2022-1932, 2024 WL 371959, at *6 (Fed. Cir. Feb. 1, 2024).

Regenxbio criticizes the District Court for not considering additional functional characteristics. Br. at 51. But Regenxbio did not raise these characteristics below. That is why the District Court did not consider them.

Regenxbio also argues that the District Court should have searched the expert reports attached as exhibits for additional characteristics – even though Regenxbio never identified any other characteristics in its briefs or at oral argument, and did not allege that any other characteristics were a basis for its contention that the Asserted Claims are patent eligible. *Id*. at 51-52. Contrary to Regenxbio's argument, the District Court was not required to search through exhibits for potential characteristics that Regenxbio did not raise in support of its arguments. As the Seventh Circuit has observed, "Judges are not like pigs, hunting for truffles buried in briefs." *United States v. Dunkel*, 927 F.2d 955, 956 (7th Cir. 1991).

2. Regenxbio Admits That the Alleged Functional Characteristics Are Not Defining Features of the Claimed Cultured Host Cells

In the District Court, Regenxbio identified only one allegedly distinguishing feature – *i.e*., some of the cultured host cells covered by the Asserted Claims ***may be*** used to make rAAV vectors for gene therapy. *See* Appx579, Appx583. However,

it is undisputed that making rAAV vectors is not a defining feature of the claimed cultured host cells. Regenxbio's argument is directly contradicted by its technical expert, Dr. Leone, who admits that "[n]one of the claims of the '617 patent say they require a gene therapy product, and certain cultured host cells infringing the claims would be ***incapable*** of creating a final gene therapy product." Appx1230 at ¶52 (emphasis added).

The additional functions listed in Regenxbio's brief, but not raised below, suffer from the same flaw. *See* Br. at 14, 35. None of the alleged characteristics are defining features of the Asserted Claims. As Dr. Leone concedes, the claimed cultured host cells simply "***do not require any functional characteristics***" at all. Appx1307 at ¶429 (emphasis added).

Notably, Regenxbio does not dispute that the alleged characteristics are not defining features of the Asserted Claims. Instead, Regenxbio contends that the alleged functional characteristics need not be features of the claimed cultured host cells for them to be considered in the determination of patent eligibility. Br. at 39-41. Regenxbio's argument is foreclosed by *Chakrabarty* and subsequent decisions of this Court – which premise the analysis of "markedly different characteristics" on the distinguishing features of the challenged claims. *See Chakrabarty*, 447 U.S. at 305-06; *ChromaDex*, 59 F.4th at 1285; *Roslin*, 750 F.3d at 1339.

In *Chakrabarty*, the Supreme Court considered markedly different functional characteristics for claimed compositions of bacteria. *See Chakrabarty*, 447 U.S. at 305. The distinguishing characteristics were readily apparent – *i.e.*, the oil metabolizing capabilities were functions that defined the claimed bacteria. *See id*. These distinguishing characteristics were found in the elements of the claims – which recited "at least two stable energy-generating plasmids" that allowed the bacteria to metabolize separate components of oil using "separate hydrocarbon degradative pathway[s]." *Id*. at 305-06.[6]

In *ChromaDex*, this Court recently affirmed the principle that "markedly different characteristics" must be defining features of the claims. In *ChromaDex*, the claims were directed to compositions containing "isolated" nicotinamide riboside ("NR"), a naturally occurring compound found in milk. *ChromaDex*, 59 F.4th at 1281. This Court found that there were no "markedly different characteristics" that distinguished the claimed compositions of "isolated" NR from

[6] The claim chart in Regenxbio's brief illustrates the striking difference between the Asserted Claims and the claims in *Chakrabarty*. *See* Br. at 25. In *Chakrabarty*, almost the entire claim is directed to the "markedly different characteristics" of the claimed bacteria. Specifically, the claims require the bacteria to have "at least two stable energy-generating plasmids." Each of those plasmids provide a unique functional characteristic – *i.e.*, a "separate hydrocarbon degradative pathway." These features are expressly recited elements that define the functional characteristics of the claimed bacteria. By contrast, the Asserted Claims do not include elements that reflect any required functional characteristics of the claimed cultured host cells – and Regenxbio does not argue that they do.

naturally occurring NR in milk, and thus, the claims were not patent eligible. *Id*. at 1284-85. The Court explained that the characteristics alleged to be distinguishing – such as enhanced bioavailability – were not defining features of the claims, and therefore, not relevant to patentability:

> The claims . . . do not ***necessarily*** require that the isolated NR be bioavailable, meaning that the claimed compositions do not ***necessarily*** possess markedly different characteristics from milk, as they ***must*** to be patent-eligible.

Id. at 1285 (emphasis added). This language is unequivocal. The alleged characteristics ***must necessarily*** be a feature of the claimed subject matter. Otherwise, they are irrelevant to the determination of patent eligibility. *Id*.

Similarly, in *Roslin*, the applicant argued that the cloned mammals recited in the claims were distinguishable from the donor mammals used to create them. *Roslin*, 750 F.3d at 1337. However, this Court found the alleged differences – based on differences in phenotype and mitochondrial DNA – were "***unclaimed***," and that "nothing in the claims, or even in the specification . . . suggests that the clones are distinct in any ***relevant*** way from the donor animals of which they are copies." *Id*. at 1338-39 (emphasis added). Thus, the Court concluded that "the claims do not describe clones that have markedly different characteristics" from the naturally occurring donor animals. *Id*. at 1339.

Here, the purportedly distinguishing characteristics of the claimed cultured host cells – such as the ability to make rAAV vectors for gene therapy – are not defining features that are found in any element of the Asserted Claims. As the District Court recognized, the Asserted Claims "simply do not reflect the distinction[s] [Regenxbio] rel[ies] on." Appx12.

Moreover, it is not enough that ***some*** of the cultured host cells within the Asserted Claims may have an allegedly distinguishing functional characteristic. Claims that are drafted broadly to encompass both purportedly patent-eligible and patent-ineligible subject matter are nevertheless invalid under §101. *ChromaDex*, 59 F.4th at 1285.

Regenxbio argues that the claimed cultured host cells need only have the "***potential*** for significant utility," again citing *Chakrabarty*. Br. at 39-40 (emphasis in original). But, this argument turns the reasoning of *Chakrabarty* on its head. The test requires the claimed subject matter to have "markedly different characteristics" – not merely the "***potential***" for such characteristics – as confirmed in *ChromaDex* and *Roslin*. Indeed, subject matter that has the "potential for significant utility" may nevertheless be patent ineligible – which undercuts Regenxbio's argument on this point. For example, Regenxbio argues that the isolated rh.10 sequences, by themselves, may be used for various purposes – such as diagnostics applications. Br. at 42. Despite their potential utility, however, the naturally occurring rh.10

sequences are indisputably not patentable subject matter. *Myriad*, 569 U.S. at 580. Thus, Regenxbio's own argument regarding the potential uses for naturally occurring AAV sequences confirms that the "potential for significant utility" is not sufficient for patentability.

Regenxbio attempts to rely on the unique characteristics and significant utility of Sarepta's cultured host cells in support of patentability. Br. at 37. But the ability of the accused cultured host cells to make rAAVs for the treatment of muscular dystrophy is not a defining feature of the claimed cultured host cells. If anything, Regenxbio's attempt to rely on the distinctive characteristics of Sarepta's cultured host cells, rather than the recited features of the Asserted Claims, only confirms that the claimed cultured host cells have no "markedly different characteristics" that support patent eligibility.

Regenxbio also argues that the Asserted Claims need not recite features of the claimed cultured host cells that are "inherent" characteristics – citing *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). Br. at 41. But unlike the applicant in *Papesch*, Regenxbio is foreclosed from arguing that the alleged functional characteristics are "inherent" in the claimed cultured host cells. Regenxbio's own technical expert admits that they are not. Appx1230 at ¶52; Appx1307 at ¶429.

Finally, Regenxbio cites *Ass'n for Molecular Pathology v. U.S.P.T.O.*, 689 F.3d 1303, 1336 (Fed. Cir. 2012) ("*AMP*"). *See* Br. at 28. In that case, the Court

determined that one disputed method claim was patent eligible because it included the step of growing a "transformed" cell – an expressly recited feature – resulting in "enhanced function and utility." *AMP*, 689 F.3d at 1336-37. Here, unlike the patent-eligible claim in *AMP*, the Asserted Claims do not reflect any allegedly distinguishing functional characteristics. The claimed cultured host cells are not "transformed" to do anything. Instead, they merely "contain."

E. The Asserted Claims Are Not a Patentable Application of the Naturally Occurring rh.10 Sequences

The Asserted Claims do not reflect a patentable application of the naturally occurring rh.10 sequences. *See Myriad*, 569 U.S. at 596; *Mayo*, 566 U.S. at 71-72, 81-87. The Asserted Claims are not related to any specific use or the treatment of any particular disease. Instead, the Asserted Claims encompass any cultured host cells containing the naturally occurring rh.10 sequences for any purpose. That is not an application sufficient for patent eligibility.

For example, in *BRCA1*, this Court found genetic testing claims that sought to capture "all comparisons between the patient's BRCA genes and the wild-type BRCA genes" to be overbroad and thus ineligible under §101, noting that "[t]he covered comparisons are not restricted by the purpose of the comparison or the alteration being detected," nor "limited to the detection of risk of breast or ovarian cancer." *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Pat. Litig.*, 774 F.3d 755, 763-64 (Fed. Cir. 2014). Indeed, the claims broadly encompassed all

comparisons for purposes "other than detection of cancer." *Id*. The Court concluded that "[s]imilar concerns to the ones the Supreme Court expressed in *Myriad* with respect to isolated DNA exist here: allowing a patent on the comparison step could impede a great swath of research relating to the BRCA genes, and it is ***antithetical to the patent laws*** to allow these ***basic building blocks of scientific research*** to be monopolized." *Id*. at 764 (emphasis added).

Here, Regenxbio argues that the Asserted Claims cover certain cultured host cells that allegedly may be used in various ways – none of which are defining features of the claimed subject matter. *See* Br. at 6, 12. According to Regenxbio, these potential uses broadly encompass (1) making copies of the naturally occurring rh.10 sequences, (2) making capsid shells and copies of the individual capsid proteins encoded by the naturally occurring rh.10 sequences, and (3) using the claimed cultured host cells for unspecified "***potential research applications***." *Id*. at 14 (emphasis added). By Regenxbio's own admission, the Asserted Claims cover ***all*** cultured host cells containing the naturally occurring rh.10 sequences for ***all*** purposes. But by broadly encompassing all possible uses, the Asserted Claims do not incorporate the naturally occurring rh.10 sequences into a patentable application. Instead, as in *BRCA1*, the Asserted Claims are an impermissible attempt to capture the entire law of nature, natural phenomenon, or abstract idea – rather than any

particular application of the ineligible subject matter that the named inventors actually developed and reduced to practice. *See BRCA1*, 774 F.3d at 764.

F. The Additional Elements Appended to the Naturally Occurring rh.10 Sequences Add Nothing New

Mayo confirms the conclusion under *Myriad* that the Asserted Claims are not a "new" composition with "markedly different characteristics." Under *Mayo*, simply appending "conventional" elements, "specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas ***cannot*** make those laws, phenomena, and ideas patentable." *Mayo*, 566 U.S. at 82 (emphasis added).

1. There Is No Dispute That the Additional Elements in the Asserted Claims Were Conventional

It is undisputed that the additional elements in the Asserted Claims are all well-known and conventional features. *See id*. at 79-80. This is confirmed by the specification, the testimony of the named inventors, and Regenxbio's technical expert, Dr. Leone, as summarized below.

Cultured Host Cells. It is undisputed that cultured host cells containing a recombinant nucleic acid molecule were well-known in the art.

- Dr. Wilson and his colleagues were not the first to make a cultured host cell containing a recombinant nucleic acid molecule. Appx876:13-877:9; Appx877:21-878:10; Appx878:11-879:2.
- As Dr. Leone acknowledges, researchers in the field of gene therapy were making and using cultured host cells "since at least the early 1980's." Appx1293-94 at ¶401.

- Dr. Leone admits that "[a] person of ordinary skill in the art would have had all the tools needed to make and use cultured host cells containing nucleic acids encoding the full scope of the claimed capsid proteins." Appx1295 at ¶404; *see also* Appx1293-95 at ¶¶401-403.

Recombinant Nucleic Acid Molecules. It is undisputed that recombinant nucleic acid molecules were conventional at the time of the '617 patent.

- Dr. Gao and Dr. Wilson both confirmed that they were not the first to make a cultured host cell containing a recombinant nucleic acid molecule encoding an AAV capsid protein. Appx864:9-16; Appx952:1-5; Appx972:15-21; Appx974:10-17.

- As Dr. Gao and Dr. Wilson testified, methods for combining nucleic acid molecules from different sources to make a recombinant nucleic acid molecule were known in the art. Appx867:3-14; Appx871:14-872:1; Appx884:21-887:9; Appx953:8-954:3; Appx1018:23-1020:7; Appx1020:9-1022:12.

- The specification describes the "assembly of selected DNA sequences" as requiring only conventional techniques. Appx178 at 25:37-47; *see also* Appx1295 at ¶403.

- And the specification directs a POSA to use known methods to introduce recombinant nucleic acids into cultured host cells. Appx178 at 25:48-51; *see also* Appx174 at 17:26-29, 18:52-57; Appx176 at 22:34:43.

Heterologous Non-AAV Sequences. It is undisputed that "heterologous non-AAV sequences" were well-known and available in the art.

- As Dr. Wilson testified, he and his colleagues did not invent "new" non-AAV sequences. Appx873:1-24; Appx874:16-875:1.

- Likewise, Dr. Gao and Dr. Wilson were not the first to combine an AAV sequence encoding a capsid protein and a heterologous non-AAV sequence into a single recombinant nucleic acid molecule. Appx882:5-883:1; Appx884:14-20.

"At Least 95% Identical" to Naturally Occurring AAV rh.10 Sequences.

It is undisputed that the element "at least 95% identical" is not an advance in the art.

- As the specification explains, methods for modifying nucleic acid sequences were conventional and well known to those skilled in the art. Appx174, 17:20-35; *see also* Appx1293-94 at ¶401.
- Dr. Gao testified that he and his colleagues did not perform any experiments to identify the 95% sequence identity threshold in the Asserted Claims. Appx988:14-16.
- Instead, as Dr. Wilson testified, the 95% limitation for sequence identity was "driven" by a discussion with "patent counsel." Appx895:23-896:13.

Combination of Elements. It is undisputed that the combination of elements in the Asserted Claims was well-known and conventional.

- Dr. Gao and Dr. Wilson were not the first to make a cultured host cell containing a recombinant nucleic acid molecule encoding an AAV capsid protein and a heterologous non-AAV sequence. Appx958:21-959:5; Appx960:12-19.
- As the specification explains, "[t]he methods used to construct any embodiment of this invention are known to those with skill in nucleic acid manipulation and include genetic engineering, recombinant engineering, and synthetic techniques." Appx174, 18:57-61; *see also* Appx177 at 24:3-6; Appx1295 at ¶403.
- Likewise, Dr. Leone admits that "conventional genetic engineering and recombinant engineering techniques were available to prepare cultured host cells containing a nucleic acid molecule encoding an AAV capsid protein." Appx1294 at ¶401.

Dependent Claims. Regenxbio argues that certain elements in the dependent claims are also a basis for patentability. Br. at 22. As an initial matter, Regenxbio never argued in the District Court that any of the dependent claims were separately

patentable. Thus, Regenxbio's arguments on appeal are waived. *See, e.g., Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 756 (Fed. Cir. 2019). But even if considered, Regenxbio's arguments contradict the undisputed statements in the specification and the admissions of the named inventors that these elements are also directed to conventional subject matter, as summarized below.

Functional Rep Genes. It is undisputed that sequences encoding functional "rep proteins" were well-known in the art and had been incorporated into recombinant nucleic acid molecules in cultured host cells.

- Dr. Gao and Dr. Wilson both testified that the AAV2 rep gene was known before the '617 patent. Appx909:14-18; Appx910:8-911:13; Appx945:12-946:7; Appx955:23-956:3; Appx975:11-23.
- They were not the first to make a cultured host cell containing a recombinant nucleic acid molecule encoding an AAV2 rep gene. Appx909:20-910:6; Appx911:14-912:4; Appx956:19-957:1.

Plasmids. It is undisputed that nucleic acid molecules in the form of a "plasmid" were well-known for delivery of sequences to cultured host cells.

- Dr. Gao and Dr. Wilson confirmed that nucleic acid molecules in the form of a plasmid were known in the art. Appx867:24-868:4, Appx868:17-21, Appx912:15-913:4; Appx956:5-10.
- They were not the first to make a cultured host cell containing a recombinant nucleic acid molecule in the form of a plasmid. Appx869:20-870:5; Appx913:5-9; Appx914:8-11; Appx956:12-17; Appx976:13-977:12; Appx978:10-17.
- Plasmids had been used to introduce nucleic acid sequences into cultured host cells long before the '617 patent. Appx868:22-869:11;

Appx913:11-14; Appx977:14-20; *see also* Appx174 at 17:20-35; Appx1295 at ¶403.

2. The Additional Elements Do Not Reflect an Advance in the Art

The admittedly conventional elements in the Asserted Claims do not reflect a patentable advance in the art. *See Mayo*, 566 U.S. at 77; *CareDx*, 40 F.4th at 1379; *Genetic Techs.*, 818 F.3d at 1375-76; *Athena*, 915 F.3d at 750-51. Instead, the specification and the testimony of Regenxbio's witnesses confirm that the focus of the claimed advance is the naturally occurring rh.10 sequences themselves.

In the '617 patent, the named inventors identify their alleged contribution as the isolation of naturally occurring AAV sequences and the preservation of those sequences – exactly as they occur in nature. *See, e.g.*, Appx166 at 1:64-66; Appx170 at 9:8-10; Appx184 at 38:2-7; Appx190 at 49:26-28. They refer to the naturally occurring variants they isolated as "novel AAV serotypes." *See* Appx166 at 1:55-2:18; Appx166-167 at 2:25-3:17; Appx167 at 3:36-44; Appx171 at 11:17-51. And they devote the vast majority of the specification to the disclosure of these allegedly "novel" AAV variants – including rh.10. *See* Appx171-174 at 11:17-17:9; Appx183-186 at Examples 1-2; Appx54-165 at Figures 1-3; Appx194-384 at SEQ ID NOS: 1-5, 9-62, 66-69, 72-113, 117-120. There is no other element in the Asserted Claims that is identified as an alleged advance in the art.

This is confirmed by the testimony of Dr. Gao, who agreed that the rh.10 sequences are the feature of the Asserted Claims that distinguish them from the prior art. Appx971:23-972:13. As Dr. Gao explained, "[t]he ***value*** here is [the] ***rhesus 10 sequence***." Appx970:19-971:12 (emphasis added). Similarly, Dr. Leone identified the "***specific sequence of AAVrh.10***" as the invention in the Asserted Claims. Appx776:19-777:2 (emphasis added); *see also* Appx777:5-12. This testimony confirms that the focus of the claimed advance is the naturally occurring rh.10 sequences – which are not patent eligible.

Regenxbio may attempt to distinguish *Mayo* as a case involving method of treatment claims. *See* Appx496-497. However, nothing suggests that the reasoning in *Mayo* applies to some types of claims, but not others. As *Mayo* explains, it is a fundamental principle that "simply appending conventional steps, specified at a high level of generality, to ***laws of nature, natural phenomena, and abstract ideas*** cannot make those ***laws, phenomena, and ideas*** patentable." *Mayo*, 566 U.S. at 82 (emphasis added). The Court did not parse out different technologies, but instead framed this principle in terms of all categories of patent-ineligible subject matter.

Regenxbio may also argue that the analysis of conventional elements is an issue for consideration only under Step 2, not Step 1, of *Alice*/*Mayo*. *See* Appx496. However, this Court has acknowledged that the conventional nature of recited elements is relevant to the analysis of both Step 1 and Step 2. *CareDx*, 40 F.4th at

1379. As this Court explained, "we have ***repeatedly analyzed conventionality at step one***." *Id*. (emphasis added). Thus, there is no "***bright line***" distinction in the analysis of conventional elements for the two steps. *Id*. (emphasis added).

The principles articulated in *Mayo* inform the analysis of "markedly different characteristics" under *Chakrabarty*. The decisions are two sides of the same coin. *Chakrabarty* requires "markedly different characteristics" for patent eligibility. *Mayo* explains that simply appending "conventional" elements "specified at a high level of generality" to patent-ineligible subject matter is not sufficient to meet the "markedly different characteristics" threshold. Both *Chakrabarty* and *Mayo* ask essentially the same question – *i.e.*, is there an alleged characteristic or advance that distinguishes the claimed subject matter as something more than just a patent-ineligible law of nature, natural phenomenon, or abstract idea. Here, the Asserted Claims fail to meet the standard for patent eligibility under either analysis.

G. Patent Eligibility Does Not Turn on the Vagaries of the "Draftsman's Art"

Regenxbio's arguments for patentability not only conflict with settled precedent under *Myriad* and *Mayo*, but also reduce patent eligibility to an exercise in claim drafting, whereby a naturally occurring DNA can be patented merely by tacking on additional "non-natural" or "genetically engineered" elements that reflect nothing more than what is already known and conventional. By applying a thin

veneer of generic elements, Regenxbio is attempting to monopolize the naturally occurring rh.10 sequences – contrary to *Myriad*.

As the Supreme Court has explained, its established precedents "warn us against interpreting patent statutes in ways that make patent eligibility '***depend simply on the draftsman's art***' without reference to the 'principles underlying the prohibition'" against patents for products of nature. *Mayo*, 566 U.S. at 72 (emphasis added). Otherwise, a patent applicant would be able to sidestep *Myriad* and monopolize a naturally occurring DNA sequence merely by drafting claims with additional, generic elements – as Regenxbio has attempted to do here – even though such elements reflect nothing more than what was already known and conventional. That would make patent eligibility an exercise in claim drafting, which "ill serve[s] the principles underlying the prohibition against patents for 'ideas' or phenomena of nature." *Flook*, 437 U.S. at 593.

H. Regenxbio Seeks to Preempt All Uses of the Naturally Occurring rh.10 Sequences in the Field of Gene Therapy

The Supreme Court has explained the rationale underlying the exceptions to patentability as a concern about preemption:

> We have described the concern that drives this exclusionary principle as one of pre-emption. Laws of nature, natural phenomena, and abstract ideas are the ***basic tools of scientific and technological work***.

Alice, 573 U.S. at 216 (emphasis added). "Monopolization of those tools through the grant of a patent might tend to ***impede innovation*** more than it would tend to promote it, ***thereby thwarting the primary object of the patent laws***." *Id*. (emphasis added); *see also Myriad*, 569 U.S. at 589; *Mayo*, 566 U.S. at 71.

But that is exactly what Regenxbio has attempted to do in this case – *i.e*., monopolize one of the "basic tools of scientific and technological work." For example, in Section I.A. of its brief, Regenxbio describes the claimed cultured host cells as an "***Important Tool***" for AAV gene therapy. Br. at 4 (emphasis added). Likewise, at the hearing on Sarepta's Safe Harbor motion, Regenxbio distinguished the claimed cultured host cells as a "***research tool***" – distinct from final, FDA-approved products. Appx1555 at 37:25-38:22 (emphasis added). And as Regenxbio's expert, Ms. Lietzan, explained, the cultured host cells are a tool used during manufacturing to contain the naturally occurring rh.10 sequences – like "***a sterile vessel***." Appx1424 at ¶58 (emphasis added).

Here, the Asserted Claims purport to cover ***any*** use of the naturally occurring rh.10 sequences in a cultured host cell for ***any*** research or commercial application – essentially removing the use of the naturally occurring rh.10 sequences as a tool for advancement in the field of gene therapy. As Regenxbio argues, "cultured host cells are ***necessary*** to the process" of creating gene therapy vectors. Br. at 36 (emphasis added). Likewise, the Asserted Claims not only cover the naturally occurring rh.10

sequences, but also any other naturally occurring sequences that are allegedly "at least 95% identical." Thus, by Regenxbio's own admission, at least one of the preemptive effects of the Asserted Claims is to block use of the naturally occurring rh.10 sequences – and naturally occurring `sequences that are "at least 95% identical" – in the research and development of new AAV vectors for gene therapy – regardless of the disease or therapeutic indication.

Moreover, as Regenxbio argues, the Asserted Claims encompass cultured host cells that are used to make copies of the naturally occurring rh.10 DNA, copies of the naturally occurring rh.10 capsid proteins expressed from that DNA, and empty rh.10 capsids that do not contain a gene of interest. Br. at 35-36. This further highlights the broad preemptive effects of the Asserted Claims.[7]

Contrary to Regenxbio's argument (Br. at 43-44), the Asserted Claims do nothing to "build" on the discovery of the naturally occurring rh.10 sequences. This is reflected in the generic elements appended to the Asserted Claims, which merely specify where the rh.10 sequences are located and how they are contained following isolation. As discussed above, Regenxbio's own witnesses concede that cultured

[7] Regenxbio argues that the Asserted Claims do not preempt all potential uses of the naturally occurring rh.10 sequences. Br. at 42-43. However, as this Court has explained, complete preemption is not required. "While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379 (Fed. Cir. 2015).

host cells with all of the additional features recited in the Asserted Claims were already well-known and conventional in the art before the '617 patent.

This is also reflected in Regenxbio's actions in this case – where Regenxbio alleged infringement of the '617 patent during Sarepta's research and development of its gene therapy products. This attempt to preempt Sarepta's innovation confirms that the Asserted Claims are nothing more than a drafting effort designed to sidestep *Myriad* and monopolize the use of naturally occurring AAV sequences, thereby inhibiting "future innovation premised upon them" – precisely the outcome that the exceptions to §101 are designed to prevent. *See Mayo*, 566 U.S. at 86.

III. The Asserted Claims Are Not Patent Eligible Under *Funk Brothers*

Regenxbio criticizes the District Court's reliance on *Funk Brothers*. Br. at 11, 29-35. However, *Funk Brothers* is a significant guidepost under §101. The decision is discussed extensively in *Myriad* and *Chakrabarty* as an important example where the minimum threshold for patentability has not been met. *Myriad*, 569 U.S. at 591; *Chakrabarty*, 447 U.S. at 310. The District Court's analysis under *Funk Brothers* is another basis for why the Asserted Claims are not patent eligible.

A. The Combination of Naturally Occurring Sequences Does Not Patentably Distinguish the Asserted Claims

In *Funk Brothers*, the Supreme Court held that claims to mixtures of naturally occurring bacteria, used to promote the growth of various leguminous plants, are not patentable. *Funk Bros.*, 333 U.S. at 132. The Court reasoned that each bacteria

species in the claimed combination "ha[d] the same effect it always had," the bacteria "perform in their natural way," and the mixture of species produced "no enlargement of the range of their utility." *Id*. at 131. As the Court explained, "once nature's secret of the non-inhibitive quality of certain strains of [bacteria] was discovered, ***the state of the art made the production of a mixed inoculant a simple step***. *Id*. at 132 (emphasis added).

Here, the Asserted Claims recite two DNA sequences, both of which are found in nature.[8] The rh.10 sequences in the Asserted Claims have exactly the same genetic information as their naturally occurring counterparts. The "heterologous non-AAV" sequences are unspecified – other than being from a non-AAV source. Merely attaching these two sequences in a single "recombinant nucleic acid molecule" does not alter their "natural functioning" or enlarge "the range of their utility." *See id*. at 131. Likewise, packaging the naturally occurring DNA sequences in a cultured host cell involved nothing more than a "simple step," given the undisputed state of the art. *See id*. at 132. Under *Funk Brothers*, the Asserted Claims have no "markedly different characteristics" that distinguish the claimed

[8] At oral argument, Regenxbio confirmed that the element "heterologous non-AAV sequence" encompasses naturally occurring sequences. Appx1432:2-7.

combination from the naturally occurring rh.10 sequences and the naturally occurring "heterologous non-AAV" sequences themselves. *See id*.[9]

Regenxbio argues that under the District Court's analysis, no claims reciting a combination of naturally occurring elements would be patentable. Br. at 32-33. That is not so. The District Court's decision is not a sweeping judgment as to all claims reciting natural occurring components. Indeed, the District Court recognized that "combinations of patent-ineligible subject matter are not necessarily invalid." Appx9. Here, the District Court evaluated the Asserted Claims under *Chakrabarty* and *Funk Brothers*. The line drawn between patent-eligible and patent-ineligible subject matter in these two cases has been the law for over 40 years. In this case, the Asserted Claims do not meet the minimum requirements for patentability.

Finally, Regenxbio argues that the District Court was "fixated" on the naturally occurring DNA sequences, rather than the claims as a whole. Br. at 33. Regenxbio is wrong. The District Court analyzed both the individual elements and the claimed combinations in the Asserted Claims. *See* Appx9 ("I begin with the 'markedly different" framework of *Chakrabarty* and consider the asserted claims in

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[9] Likewise, dependent claims reciting an "AAV2 rep gene" are not patent eligible, contrary to Regenxbio's argument. *See* Br. at 22. Both Dr. Gao and Dr. Wilson confirmed that the AAV2 rep gene is a naturally occurring sequence that was known in the art. *See* Section II.F.1, *supra*. Adding a third, naturally occurring sequence to the recombinant nucleic acid molecule in the Asserted Claims does not result in any "markedly different characteristics." *Funk Bros*., 333 U.S. at 132.

their entirety."). If anything, it is Regenxbio who fails to evaluate the claim language as a whole – by overemphasizing selected elements that it contends are "not naturally occurring," "genetically engineered," or "created in the lab," yet at the same time, all but ignoring the only element in the Asserted Claims that actually relates to what the named inventors considered to be their contribution to the art – the isolation of naturally occurring rh.10 sequences. No matter how they are analyzed, the Asserted Claims are deficient.

B. During Prosecution, the Examiner Rejected Regenxbio's Argument That the Formation of a "Recombinant" DNA Molecule Is Sufficient for Patent Eligibility

Regenxbio argues that the decision in this case is inconsistent with an example in a PTO guidance issued in 2014 – relating to a "recombinant" nucleic acid vector. Br. at 47-48. However, as discussed above, the Examiner considered the applicant's amendment of the pending claims to recite a "recombinant" nucleic acid molecule during prosecution of the '617 patent. *See* Section II.C., *infra*. The Examiner determined that the generic "recombinant nucleic acid molecule" in the pending claims was not structurally or functionally different for purposes of patentability from the naturally occurring rh.10 sequences themselves. Appx654. Thus, contrary to Regenxbio's argument, the decision in this case will not upend "decades" of patent practice under the PTO guidance, but instead, is fully consistent with the Examiner's assessment of the term "recombinant," as it is used in the Asserted Claims.

The 2014 PTO guidance expressly cautions that the examples must be interpreted in light of the specific facts, and that different fact patterns may have different outcomes as to ineligibility. *See* Appx678. Moreover, the PTO guidance is not binding on this Court. In *Myriad*, the Supreme Court rejected a similar argument regarding past Patent Office practice when it held that "isolated" DNA sequences are not patent eligible. *Myriad*, 569 U.S. at 593-94; *see also In re Rudy*, 956 F.3d 1379, 1382-83 (Fed. Cir. 2020). The same reasoning applies here, particularly where Regenxbio's argument regarding an example in the guidance conflicts with an express determination by the Examiner during prosecution. In light of the prosecution history, the cited example in the PTO guidance is inapposite.

IV. The Asserted Claims Are Not Patent Eligible Under the Two-Part Test of *Alice*/*Mayo*

Alice/*Mayo* also confirms that the Asserted Claims are not patent eligible.

A. The Undisputed Facts Show That the Asserted Claims Are "Directed To" Unpatentable Subject Matter

For the reasons discussed above, the "focus of the claimed advance" is the isolation of the naturally occurring rh.10 sequences. *See Genetic Techs.*, 818 F.3d at 1375-76. Thus, the Asserted Claims are "directed to" patent-ineligible subject matter, and Step 1 is satisfied.

B. Regenxbio Does Not Dispute That There Is No "Inventive Concept"

The additional elements in the Asserted Claims do not transform the naturally occurring rh.10 sequences into patent-eligible subject matter. Regenxbio has never attempted to identify an "inventive concept" or to rebut the facts underlying this conclusion. *See* Br. at 17-19, 44-46. Thus, Step 2 is undisputed, and the Asserted Claims are patent ineligible under *Alice*/*Mayo*.

Regenxbio argues that it was error for the District Court to apply *Alice*/*Mayo*. Br. at 44. However, the District Court followed the analysis of this Court in *ChromaDex*, and evaluated the Asserted Claims two ways – for "markedly different characteristics" under *Chakrabarty* and under the two-part test of *Alice*/*Mayo*. The Asserted Claims are not patent eligible under either test.

Regenxbio also argues that District Court erred in its analysis of Step 2 because it considered only the methods used to make the claimed cultured host cells, but not the elements in the claimed combinations. Br. at 12-13. Regenxbio is wrong. The District Court expressly considered the elements in the Asserted Claims: "The claims themselves do not include an inventive concept. I also do not think that the specification reveals an inventive concept in the claims." Appx12 (citation omitted). As the District Court noted, Regenxbio never "advanced any arguments to the contrary." Appx13.

By considering Step 2 at all, the District Court actually gave Regenxbio another chance to explain why the Asserted Claims are patent eligible. But Regenxbio failed to do so. Regenxbio's inability to show an "inventive concept" demonstrates that it cannot explain what the alleged advance in the Asserted Claims actually is – beyond the isolation of the naturally occurring rh.10 sequences. The District Court's analysis under *Alice*/*Mayo* – based on the unrebutted facts – is yet another reason why the judgment should be affirmed.

V. The District Court Made No Factual Inferences, in Light of the Undisputed Record

Regenxbio argues that two purported factual inferences in the District Court's analysis warrant remand. Br. at 49-52. But the District Court did not make any factual inferences to determine that the Asserted Claims are not patent eligible. Here, the material facts are undisputed. At oral argument, Regenxbio agreed that there was no disputed issue of fact that precluded summary judgment. Appx1429:17-1430:3. Likewise, there is no fact issue for remand.

First, Regenxbio argues that the District Court adopted Sarepta's argument "that the cultured host cells are no more than a container for genetic material." Br. at 50-51. But that is exactly what the Asserted Claims say. The only recited feature of the claimed cultured host cells is that they "contain" the recombinant nucleic acid molecule. This function is reflected in the transition phrase "containing" in each of the Asserted Claims. And Regenxbio never proposed any construction to change

the plain meaning of the word "containing." The District Court did not need to draw any factual inference to understand the express language of the Asserted Claims.

Likewise, the District Court did not make any factual inference regarding the only alleged functional characteristic of the claimed cultured host cells – to make rAAV vectors for gene therapy. *See* Appx11-12. As discussed above, the District Court determined that this alleged characteristic is not a defining feature of the Asserted Claims, and therefore, is irrelevant to patentability. Appx12 (quoting *ChromaDex*, 59 F.4th at 1285).

The facts underlying this determination are undisputed. The District Court found that there is nothing in the claim language or specification that limits the recited cultured host cells to those that are capable of making rAAV vectors. Appx11-12. Regenxbio did not dispute this determination. *See* Appx11 ("Plaintiffs do not point to anything in the claims or specification that requires utility for gene therapy."). Indeed, as the District Court noted, Dr. Leone admitted that "some of the claimed embodiments ***cannot even be used for gene therapy***." Appx11-12 (emphasis added). The District Court did not need to make any factual inference to reach its conclusion that the claimed cultured host cells do not require utility for gene therapy. Thus, there is no fact issue for remand.

Second, Regenxbio argues that the District Court failed to consider other "potential utilities" for the claimed cultured host cells – besides gene therapy. Br. at

51. However, as discussed above, Regenxbio never raised any other alleged uses for the claimed cultured host cells in the District Court. These are new arguments that Regenxbio has made for the first time on appeal. That is the reason why the District Court did not consider them. As such, these arguments are waived.

But even if they are not, the newly-alleged uses do not make any difference to the outcome. Like the alleged use for gene therapy, none of the potential uses that Regenxbio raises for the first time on appeal are defining features of the claimed cultured host cells. Regenxbio does not contend that they are. Thus, it is undisputed that these additional alleged uses do not distinguish the subject matter in Asserted Claims. No remand is warranted on this basis either.

VI. Affirmance Will Not Have Far-Reaching Consequences

Regenxbio argues that the District Court's decision conflicts with "settled expectations." Br. at 46-48. However, the decision in this case does not have such far-reaching implications. The District Court's conclusion that the Asserted Claims are not patent eligible is simply the application of well-established precedents under §101. As discussed above, the Asserted Claims fail to meet the threshold for patentability no matter how they are analyzed – under the "markedly different characteristics" test using the reasoning in *Myriad*, *Chakrabarty*, or *Funk Brothers*, or under the two-part test of *Alice*/*Mayo*. Reversal in this case would be a sharp departure from these established precedents.

Moreover, the District Court's decision fully aligns with the policies underlying the exceptions to §101 by preventing Regenxbio from monopolizing a basic tool of scientific research – naturally occurring rh.10 sequences – thereby promoting innovation and further scientific advances based upon them. *See Myriad*, 569 U.S. at 589; *Alice*, 573 U.S. at 216.

Regenxbio also argues that the District Court's decision is inconsistent with "settled expectations" based on one example in a 2014 guidance from the PTO – regarding a "recombinant" nucleic acid vector. Br. at 47-48. But as discussed above, the Examiner considered this issue during prosecution. The Examiner found that the applicant's amendment of the pending claims to add the term "recombinant" did not overcome the rejection for patent ineligibility. *See* Appx650-655. Here, the prosecution history overrides any purported "settled expectations" that Regenxbio or others may have had regarding the patentability of the "recombinant" nucleic acid molecule in the Asserted Claims.

At bottom, Regenxbio asks this Court to adopt a new standard of patent eligibility that overturns *Myriad*. In that regard, Regenxbio cites testimony from a Senate Judiciary Committee hearing in January 2024 regarding statutory amendments to §101 that would do just that. Br. at 46-47. At the hearing, the Committee heard witnesses on both sides regarding the pros and cons of the proposed amendments, and the implications for innovation and competitiveness in

the United States. Contrary to the suggestion in Regenxbio's brief, these questions are actively debated.

Evidence presented at the hearing shows that the current standard for patent eligibility under *Myriad* has not led to grave consequences for the biotechnology industry, as Regenxbio contends, but if anything, has resulted in greater innovation through the sharing of basic scientific information, and has actually increased capital investment in research and development overall. *See* www.judiciary.senate.gov/download/2024-01-23-testimony-blaylock. Indeed, many groups oppose changes to the current standard for patent eligibility under *Myriad* – including civil rights, medical, scientific, technology, patient advocacy, and environmental organizations – and have made their opposition known to the current administration. *See*, *e.g.*, www.aclu.org/node/99618.[10]

[10] Amici AIPLA and PICI argue that a multitude of calamities will befall the biotechnology industry if compositions such as the claimed cultured host cells are not patent eligible. *See* AIPLA Br. at 13-17; PICI Br. at 30-38. But the District Court did not go beyond established precedent and declare that all such compositions are not patentable. Instead, the District Court focused its analysis and conclusions on the Asserted Claims in this case. Appx9-13. Every other composition that AIPLA and PICI fear would be unpatentable must be analyzed on its own merits. Moreover, the Supreme Court has warned against departing from its precedent "lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another." *Mayo*, 566 U.S. at 92. Accordingly, the Asserted Claims must be examined under existing precedent and, as in *Mayo*, this Court "need not determine here whether, from a policy perspective, increased protection for discoveries [in the field of biotechnology] is desirable." *Id*.

In any event, resolution of this policy debate is not an issue to be decided here. As this Court well understands, any amendments to §101 are for Congress to debate. It is not the province of the Court to weigh the pros and cons of such proposals. As such, Regenxbio's arguments about alternative standards for patent eligibility are entitled to no weight when deciding the narrow issue in this appeal.

CONCLUSION

For all the reasons discussed above, the District Court correctly determined that the Asserted Claims are invalid under §101. The judgment should be affirmed.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B)(i) and Federal Circuit Rule 32(b)(1) because, excluding the portions exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rule 32(b)(2), it contains 13,979 words as counted by the word processing program used to prepare the brief.

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared using Microsoft Office Word in a proportionally spaced typeface: Times New Roman, 14-point font.

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